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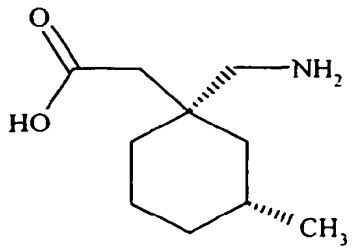
(54) Use of a gabapentin-analog for the manufacture of a medicament for preventing and treating visceral pain

(57) [1S-(1α,3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid is useful to prevent and treat visceral pain.



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venting or treating visceral pain and gastrointestinal disorders, in particular by the oral route.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The compound used in the instant invention, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid (Formula I above), is described in international patent application WO 97/33858 which is incorporated herein by reference, and which more generally describes substituted derivatives of gabapentin, including [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid; such derivatives bind to the $\alpha_2\delta$ subunit of a calcium channel, and are useful in the treatment of epilepsy. In that application WO 97/33858, the compound utilized in the instant invention has been shown to have an affinity similar to that of gabapentin for the $\alpha_2\delta$ subunit derived from porcine brain tissue.

[0010] It has now been found that [IS-(la, 3 (3)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, although of similar activity or less active than gabapentin on somatic pain or epilepsy, is surprisingly ten-fold more effective than gabapentin on visceral pain.

This finding is at odds with the well recognized knowledge that, at every level of the nervous system, a close relationship prevails between somatic pain pathways and visceral pathways (Cross S.A. (1994) Mayo Clin Proc **69**: 375-83).

[0011] The compounds utilized in the present invention include solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the compound of Formula I.

[0012] Where it is appropriate to form a salt, the pharmaceutically acceptable salts include acetate, benzenesulfonate, benzoate, bitartrate, calcium acetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycoloylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydrogencarbonate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate or hemi-succinate, sulfate or hemisulfate, tannate, tartrate or hemi-tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, ammonium, tetramethyl ammonium, calcium, lithium, magnesium, potassium, sodium, and zinc. (See also "Pharmaceutical salts" by Berge S.M. *et al.* (1997) J. Pharm. Sci. **66**: 1-19, which is incorporated herein by reference.)

[0013] The term "patient" is intended to include a mammal, especially a human.

[0014] All that is required to practice the method of preventing and treating visceral pain and GI disorders FBD or IBD according to the present invention is to administer [1S-(1α,3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid in an amount that is effective to prevent or treat the damaged condition, i.e. to control visceral pain and/or FBD or IBD. The effective amount of [1S-(1α,3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid to be utilized will generally be from about 1 to about 300 mg / kg of patient body weight. Typical doses will be from about 10 to about 5000 mg per day for an adult patient of normal weight. Typical FBD conditions include gastro-esophageal reflux disease, dyspepsia, and IBS. Typical IBD conditions include ileitis, ulcerative colitis, and Crohn's disease.

[0015] In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of visceral pain and GI disorders comprising the active component, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, of Formula I. Pharmaceutical compositions of the compound of the present invention -including one of its salts, are produced by formulating this active component in dosage unit form with at least one pharmaceutically acceptable carrier or excipient. For preparing pharmaceutical compositions from the compound used in this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.

[0016] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. They preferably contain 5% to about 70% of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid. In such solid dosage forms, the active component is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol. (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0017] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose as well as high molecular weight polyethyleneglycols, and the like.

[0018] Solid dosage forms such as tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They can also be of such composition that they release the active component in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions

L.O. and Sellitto J.J. (1957) Arch. Int. Pharmacodyn. **4**: 409-419). Male Sprague Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat and nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent any tissue damage to the paw. On the test day, two to three baseline measurements were taken before animals were administered 100 µl of 2% carrageenin by intraplantar injection into the right hind paw. Nociceptive thresholds were taken again 3 h after carrageenin to establish that animals were exhibiting hyperalgesia. Animals were dosed with either gabapentin, [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid, or saline at 3.5 h after carrageenin, and nociceptive thresholds were examined at 4, 4.5, and 5 h post-carrageenin.

Results

[0031] Effect of gabapentin

***Dose p.o.* (mg/kg)**	**Inhibition at 1 h (%)**	**Inhibition at 2 h (%)**
30	48	20

[0032] Effect of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid:

Dose *p.o.* (mg/kg)	**Inhibition at 1 h (%)**	**Inhibition at 2 h (%)**
30	68	34

Epilepsy:

Semicarbazide-induced tonic seizures in mice: effect of gabapentin and [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid

[0033] Tonic seizures in mice are induced by subcutaneous administration of semicarbazide (750 mg/kg). The latency to the tonic extension of forepaws is noted. Any mice not convulsing within 2 h after semicarbazide are considered protected and given a maximum latency score of 120 min.
At the same dose of 30 mg/kg *p.o.*, gabapentin protected 100% of the animals whereas [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid protected 40%.

Visceral pain:

TNBS-induced chronic visceral allodynia in rats: effect of gabapentin and [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid

[0034] Injections of trinitrobenzene sulfonic acid (TNBS) into the wall of the rat colon have been found to induce chronic colitis. In humans, GI disorders are often associated with visceral pain. In these pathologies, the visceral pain threshold is decreased indicating a visceral hypersensitivity. This study was designed to evaluate the effect of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid *p.o.* in an experimental model of colonic distension in awake rats; previous injection of TNBS into the proximal colon of the rats had lowered their visceral pain threshold. This effect is compared with that of gabapentin *p.o.*

Materials and methods

[0035] Male Sprague-Dawley rats weighing 340-400 g are used. The animals are housed 3 per cage in a regulated environment (20 ± 1°C, 50 ± 5 % humidity, with light 8:00 am to 8:00 pm). At day 0, under anesthesia (ketamin 80 mg/kg *i.p.*; acepromazine 12 mg/kg *i.p.*), the injection of TNBS (50 mg/kg in ethanol 30 %), or saline (1.5 ml/kg) for control rats, is performed into the proximal colon wall (1 cm from the cecum). After the surgery, animals are individually housed in polypropylene cages and kept in a regulated environment (20 °C, 50 % humidity, with light 8:00 a.m. to 8: 00 p.m.) during 7 days. At day 7 after TNBS administration, a balloon (5-6 cm length) is inserted by anus, and kept in position (tip of balloon 5 cm from the anus) by taping the catheter to the base of the tail. Oral administration of gabapentin or of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid is performed 1 h before the colonic distension cycle: the balloon is progressively inflated by steps of 5 mm Hg (0.667 kPa), from 0 to 75 mm Hg, each step of inflation lasting 30 s. Each cycle of colonic distension is controlled by a standard barostat. The threshold (mm Hg) corresponds

acetic acid is observed following oral administration of the compound.

Claims

1. A method for preventing visceral pain comprising administering to a patient in need of treatment an effective amount of [1S-(1α,3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

2. A method for treating visceral pain comprising administering to a patient in need of treatment an effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

3. A method for preventing gastrointestinal disorders comprising administering to a patient in need of treatment an effective amount of [1S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

4. A method for treating gastrointestinal disorders comprising administering to a patient in need of treatment an effective amount of [1S-(1α,3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof.

5. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is characterized as functional bowel disorder or inflammatory bowel disease.

6. A method according to Claim 3 or Claim 3 wherein the gastrointestinal disorder is a functional bowel disorder.

7. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is gastro-esophageal reflux disease.

8. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is dyspepsia.

9. A method according to Claim 3 or Claim 4 wherein the gastrointestinal disorder is the irritable bowel syndrome.

10. A method according to Claim 3 or Claim 4 wherein the condition treated is selected from Crohn's disease, ileitis, and ulcerative colitis.

11. A method according to Claim 3 or Claim 4 wherein [1S-(1α,3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof is administered by the oral route.

12. The use of [1 S-(1α, 3β)]-(1-aminomethyl-3-methyl-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful for preventing or treating visceral pain.

13. The use according to claim 12 wherein the medicament is a formulation for oral administration.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 40 0440

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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12-10-1999

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